Determinants in HIV-2 Env and tetherin required for functional interaction.

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Authors: Colin M Exline, Su Jung Yang, Kevin G Haworth, Srinivas Rengarajan, Lisa A Lopez, Magali E Droniou, Eduardo Seclen, Paula M Cannon

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Public Summary:
The protein tetherin is a human antiviral factor that inhibits the release of lentiviruses. In order to be released from the cell, some viruses have developed different strategies to counteract tetherin function. In the case of HIV-2, the envelope (Env) protein sequesters tetherin through a mechanism that is not fully characterized. In this paper, we have mapped an alanine face in tetherin that is required for the Env-tetherin interaction, and showed that specific regions of Env can influence this interaction (ectodomain and cytoplasmic tail). We have also shown that HIV-2 can reacquire the ability to block alanine-mutated tetherin when passaged in culture by adapting its cytoplasmic tail. These results illustrate the importance of the anti-tetherin activity for viral fitness.

Scientific Abstract:
BACKGROUND: The interferon-inducible factor BST-2/tetherin blocks the release of nascent virions from the surface of infected cells for certain enveloped virus families. The primate lentiviruses have evolved several counteracting mechanisms which, in the case of HIV-2, is a function of its Env protein. We sought to further understand the features of the Env protein and tetherin that are important for this interaction, and to evaluate the selective pressure on HIV-2 to maintain such an activity. RESULTS: By examining Env mutants with changes in the ectodomain of the protein (virus ROD14) or the cytoplasmic tail (substitution Y707A) that render the proteins unable to counteract tetherin, we determined that an interaction between Env and tetherin is important for this activity. Furthermore, this Env-tetherin interaction required an alanine face in the tetherin ectodomain, although insertion of this domain into an artificial tetherin-like protein was not sufficient to confer sensitivity to the HIV-2 Env. The replication of virus carrying the ROD14 substitutions was significantly slower than the matched wild-type virus, but it acquired second-site mutations during passaging in the cytoplasmic tail of Env which restored the ability of the protein to both bind to and counteract tetherin. CONCLUSIONS: These results shed light on the interaction between HIV-2 and tetherin, suggesting a physical interaction that maps to the ectodomains of both proteins and indicating a strong selection pressure to maintain an anti-tetherin activity in the HIV-2 Env.